General

Guideline Title

Approach to fever assessment in ambulatory cancer patients receiving chemotherapy.

Bibliographic Source(s)

Krzyzanowska MK, Walker-Dilks C, Atzema CL, Morris A, Gupta R, Halligan R, Kouroukis CT, McCann K, Fever Assessment Expert Panel. Approach to fever assessment in ambulatory cancer patients receiving chemotherapy. Toronto (ON): Cancer Care Ontario (CCO); 2015 Nov 27. 67 p. (Program in Evidence-based Care Guideline; no. 12-15). [78 references]

Guideline Status

This is the current release of the guideline.

The Program in Evidence-based Care (PEBC) guideline, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario (CCO) Web site for details on any new evidence that has emerged and implications to the guidelines.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

1. Temperature: Cancer patients in the community receiving chemotherapy who experience a fever should be assessed. While fever is not a reliable predictor of unfavourable outcomes such as febrile neutropenia, infection, or death, it is a serious symptom.
    a. A fever is defined as an oral temperature of ≥38.3°C or sustained temperature of 38.0°C lasting more than one hour.
    b. Tympanic temperature measurement is a viable option and should be measured according to manufacturers' specifications.
2. Assessment: Patients with fever should seek urgent assessment. Insufficient evidence exists to make specific recommendations with respect to the timing, location, or personnel involved in the assessment of fever in the target population.
    a. If fever occurs outside of clinic hours, the current practice of referring patients who have developed a fever to the emergency department is the only tenable option in many communities.

3. Education: Cancer patients receiving chemotherapy in the outpatient setting should be provided with standardized information about fever and fever-associated infection.
    a. Patients should be informed about how to measure their temperature and how to recognize when assessment by a healthcare provider is recommended.
    b. This information should be delivered at the time of chemotherapy initiation and may be provided in conjunction with other self-assessment education, and reinforced with take-home written material and communication with healthcare providers.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

- Fever induced by chemotherapy
- Cancer

Guideline Category

Evaluation

Management

Risk Assessment

Clinical Specialty

Emergency Medicine

Family Practice

Hematology

Internal Medicine

Nursing

Oncology

Intended Users

Advanced Practice Nurses

Hospitals

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To provide advice regarding the assessment of fever in cancer patients in the community who are receiving chemotherapy, given the potential for serious complications that is associated with it:

To investigate whether there are predictors that are associated with a poor outcome
To determine where and how quickly the assessment should take place for these patients and who can/should perform the assessment
To determine what advice, information, or education should be provided to patients receiving chemotherapy in the community should they develop a fever

Target Population

Adult patients with cancer (i.e., solid tumours or lymphoma) receiving chemotherapy in an outpatient setting who have a fever at home

Note: Emergency department, in-hospital, and outpatient management of febrile neutropenia or serious infection are beyond the scope of the guideline (see Table 1-1 in the original guideline document for a complete summary of target population). Patients who have had hematopoietic stem cell transplantation or who have acute leukemia or myelodysplastic syndrome are excluded secondary to the pathophysiologic differences in prognosis in the setting of fever.

Interventions and Practices Considered

1. Temperature measurement
2. Seeking urgent assessment at clinic/emergency department (if fever is present)
3. Chemotherapy patient education on fever and fever-associated infection

Major Outcomes Considered

- Temperature and risk for poor outcome
- Clinical predictors for the development of febrile neutropenia/Multinational Association for Supportive Care in Cancer (MASCC) score
- Relationship between the timing or location of fever assessment, or the personnel doing the fever assessment, and the outcome of a fever episode
- Effect of information or education provided to patients
- Sensitivity and specificity of clinical predictors

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Search for Existing Guidelines

A search for existing guidelines is generally undertaken prior to searching for existing systematic reviews or primary literature. This is done with the goal of identifying existing guidelines for adaptation or endorsement in order to avoid the duplication of guideline development efforts across jurisdictions.

For this document, a search was conducted of the Search Standards and Guidelines Evidence (SAGE) Directory of Cancer Guidelines (www.cancerview.ca) and the National Guideline

Clearinghouse (NGC). In addition, the Web sites of several known high-quality guideline developers, including the American Society of Clinical Oncology (ASCO), the National Institute for Health and Care Excellence (NICE), and the Infectious Diseases Society of America (IDSA) were searched. Citations to guidelines were also retrieved in the literature search of MEDLINE and EMBASE. Guidelines that were considered relevant to the objectives and the research questions were then evaluated for quality using the Appraisal of Guidelines Research and Evaluation II (AGREE II) instrument (http://www.agreetrust.org /).

Literature Search Strategy

A literature search of the MEDLINE and EMBASE databases was conducted and covered the years from database inception to March 2014. The search strategies combined terms for fever, cancer, chemotherapy, outpatients, emergency care, and information. Separate searches were conducted to focus on risk assessment and body temperature. The search strategies are in Appendix 3 in the original guideline document. The Cochrane Library was also searched and references of relevant retrieved articles were scanned.

An updated search was run to retrieve any relevant articles between March 2014 and November 2015.

Study Selection Criteria and Process

Retrieval from the MEDLINE/EMBASE searches was exported to EndNote. The research methodologist reviewed the titles and abstracts that resulted from the searches. For those items that warranted full-text review, the research methodologist reviewed each item independently and conferred with the Working Group members.

Articles (full-text reports or conference abstracts) were considered for inclusion according to their study design and relevance to the research questions. The research questions pertained to risk factors, prediction models, and relationships rather than management of the fever; therefore, prospective or retrospective studies with at least 30 participants were eligible for inclusion. All studies were required to include cancer patients receiving chemotherapy. Systematic reviews containing studies meeting these criteria were also considered.

For each research question, studies also had to meet the following criteria:

- How does temperature relate to risk for febrile neutropenia, serious infection, or death?
  - Studies that compared patients with different cut-offs of temperature and evaluated risk for unfavourable outcome (e.g., febrile neutropenia, serious infection, hospital admission, or death) or investigated the measurement of temperature were eligible.
- What are the clinical predictors for the development of febrile neutropenia?
  - Studies of clinical prediction rules with the generation of the rule in one or more sets of patients (derivation set) and testing the rule in another set of real patients (validation set) were eligible. A study could also validate an already developed rule in a new set of patients. Studies with bootstrapped validation sets (derivation and validation sets taken from the same patient population) were excluded. The criteria for assessing these studies were based on the Journal of the American Medical Association (JAMA) Users' guides to the medical literature article on clinical decision rules.
- What is the relationship between the timing or location of fever assessment, or the personnel doing the fever assessment, and the outcome of a fever episode?
  - Prospective or retrospective studies of patient assessment focusing on location, timing, or personnel doing the assessment that evaluated the risk for unfavourable outcome
- Do the type, quantity, and content of information provided to patients affect their choice about when and where to seek care for fever?
  - Prospective or retrospective studies of education or information about managing fever provided to patients or care givers

Studies that included patients considered to be high risk (i.e., hematopoietic stem cell transplantation, acute leukemia, and myelodysplastic syndrome) and studies of infants, children, or adolescents were

excluded.

Literature Search Results

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram showing the literature retrieval process and results is in Appendix 4 in the original guideline document. Of the 119 articles that were assessed for eligibility, 45 were included. The majority of excluded articles were ineligible because they were non-systematic reviews, studies that did not address a study question, or studies that described clinical prediction rules but did not contain a validation set of patients. Of the 45 included articles, seven were guidelines or summaries of guidelines that have been described above.

Studies were categorized by the research question to which they pertained.

Number of Source Documents

Forty-five studies were included in the qualitative synthesis:

- Research Question 1: 7 studies
- Research Question 2: 15 studies
- Research Question 3: 16 studies
- Research Question 4: 6 studies

Three studies addressed questions 1 and 2; another three studies addressed questions 3 and 4. See Appendix 4 in the original guideline document for a PRISMA flow diagram of the literature search.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Data Extraction and Assessment of Study Quality and Potential for Bias

Data extraction was performed by the research methodologist. Important quality features such as study design, study setting, patient numbers and characteristics, description of risk factors or interventions, and outcomes were extracted for each study. Since randomized, nonrandomized, diagnostic, and clinical prediction studies were included in this review, no specific quality assessment tool was used.

Synthesizing the Evidence

Because of the differences among study designs, outcomes assessed, and results reported, meta-analysis was not feasible.

Study Design and Quality

The nature of the research questions determined the types of study designs that were included. For the most part, answers to the study questions were not amenable to intervention studies (for ethical reasons); thus, a validated risk of bias tool was not used to perform quality assessment. The quality of the evidence was generally low. Many studies were not comparative, making an evaluation of benefits and harms difficult. Eleven studies were reported in conference abstracts. The topics of these studies were relevant to the research questions, but in most cases insufficient information was provided about design issues or study details to fully evaluate the study quality. Few studies directly addressed the topic of fever except as one among many symptoms or adverse effects associated with chemotherapy.

Studies pertaining to question 1 were mostly designed as diagnostic accuracy studies, but only one included blinded interpretation of clinical predictors. Studies pertaining to question 2 were clinical prediction rules. For most of these studies, the performance of the risk score was evaluated by conducting an accuracy study with calculation of sensitivity, specificity, and positive and negative predictive values. Blinded assessment of predictor variables or outcomes was not reported in any of the studies. Studies pertaining to questions 3 and 4 were mainly case series or surveys with no comparison groups. Of the four randomized controlled trials (RCTs) identified, one described allocation concealment.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Guideline Developers

This guideline was undertaken by the Fever Assessment Guideline Development Group (GDG), a group organized by the Program in Evidence-based Care (PEBC) at the request of the Cancer Care Ontario (CCO) Systemic Treatment Program. The group was comprised of two medical oncologists, one malignant hematologist, one emergency physician, one infectious diseases physician, one primary care physician, one nurse practitioner, and one PEBC methodologist plus an Expert Panel comprised of medical oncologists, pharmacists, advanced practice nurse, and patient advisor.

The project was led by a small subcommittee, referred to as the Working Group from this point forward, whose members were responsible for creating the evidence base, drafting the first version of the recommendations, and leading the response to the external review. All members of the GDG contributed to final interpretation of the evidence, refinement of the recommendations, and approval of the final version of the document.

Guideline Development Methods

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle. This process includes a systematic review, interpretation of the evidence by the Working Group and draft recommendations, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders.

The PEBC uses the Appraisal of Guidelines Research and Evaluation II (AGREE II) framework as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence base. This is described in the *PEBC Document Assessment and Review Protocol* (see the "Availability of Companion Documents" field). PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation; however, a list of implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more

detail in the PEBC Handbook and the PEBC Methods Handbook (see the "Availability of Companion Documents" field).

Research Questions

The Working Group of the Fever Assessment Guideline Development Group (GDG) developed this evidentiary base to inform recommendations as part of a clinical practice guideline. Based on the objectives of this guideline, the Working Group derived the research questions outlined below.

> How does temperature relate to risk for febrile neutropenia, serious infection, or death?
> What are the clinical predictors for the development of febrile neutropenia?
> What is the relationship between timing or location of fever assessment, the personnel doing the fever assessment, and the outcome of a fever episode?
> Do the type, quantity, and content of information provided to patients affect their choice about when and where to seek care for fever?

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Guideline Review and Approval

Internal Review

For the guideline document to be approved, 75% of the content experts who comprise the Guideline Development Groups (GDG) Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the Program in Evidence-based Care (PEBC) Report Approval Panel (RAP), a three-person panel with methodology expertise, must unanimously approve the document. The Expert Panel and RAP members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external review, then the revised draft must be resubmitted for approval by RAP and the GDG Expert Panel.

External Review

Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise are identified by the GDG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other potential users of the guideline are contacted and asked to provide feedback on the guideline recommendations through a brief online survey. This consultation is intended to facilitate the dissemination of the final guidance report to Ontario practitioners.

See Section 5 in the original guideline document for further discussion of the internal and external guideline review process and results.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The recommendations are supported by existing guidelines; randomized, nonrandomized, diagnostic, and clinical prediction studies; and consensus.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Improved assessment of ambulatory cancer patients developing fever while receiving chemotherapy

Potential Harms

Although urgent assessment of patients who develop a fever at home may lead to unnecessary hospital visits, long wait times, exposure to other sick patients, unnecessary use of antibiotics, and patient anxiety, the benefits conferred by urgent assessment currently outweigh the potential harms of febrile neutropenia complications and risk of death.

Contraindications

Contraindications

Administration of antipyretic medication may mask the presence of fever and should be avoided if possible.

Qualifying Statements

Qualifying Statements

- Overall, the evidence on the management of fever in cancer patients receiving chemotherapy before they present to the emergency department was of low quality and most was not directly related to the research questions. Existing guidelines focused on the management of febrile neutropenia after it was diagnosed, with limited information on the pre-diagnosis assessment. The primary literature provided limited evidence because most studies addressed the adverse effects of chemotherapy without a specific emphasis on fever. Few studies were comparative, and many were conference abstracts, providing insufficient detail on which to draw definitive conclusions.
- Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario (CCO) makes no representation or guarantees of any kind whatsoever regarding

the report content or use or application and disclaims any responsibility for its application or use in any way.
- See the original guideline document for qualifying statements related to each specific recommendation.

Implementation of the Guideline

Description of Implementation Strategy

Implementation Considerations

There is concern in Ontario that there is over-use of emergency department services by cancer patients who develop fever while undergoing chemotherapy. One goal of this guideline was to determine whether alternate care paths could be supported by research evidence. At the present time, the conclusion reached here is that there is insufficient evidence to predict with certainty which patients who develop fever are at risk of poor outcome, and therefore all patients should be assessed, given the serious consequences of infection. In other words, there is no way to define what constitutes "over-use" of emergency department services; therefore, recommendations to reduce that use are not possible at present.

Despite lack of studies to define optimal models of care for patients receiving chemotherapy who experience a fever, the Guideline Panel identified some evidence that could be used to guide future practice. Predictive models that have been developed and validated in patients already diagnosed with febrile neutropenia, such as the Multinational Association for Supportive Care in Cancer (MASCC) score, could be incorporated into assessment algorithms for chemotherapy patients with fever to identify low-risk patients that could be safely assessed outside the emergency department. This would require concomitant data collection to confirm the validity of this approach and provide much needed evidence to inform practice. There are also emerging data on the feasibility and efficacy of remote management of chemotherapy-related symptoms using technology and phone-based strategies. Participation in such studies is highly encouraged so that evidence can be generated to inform models of care.

One of the issues identified during the course of this guideline's development is that there is a lack of standardization of the information provided to patients regarding what to do if they experience a fever. The Guideline Panel believed patients should be effectively educated to expect the potential adverse events during and following chemotherapy treatment, including fever and the consequences of infection. They should understand what fever is, how to measure it, and where to go for assistance. Innovative strategies should be considered to support their care, such as having a dedicated on-call nurse through the systemic treatment clinic, or community services through pharmacies or laboratories. Technological advancements in obtaining a definitive neutrophil count at home or in the community may be possible in the near future.

It is essential that knowledge transfer regarding fever assessment involves all healthcare personnel who care for cancer patients receiving chemotherapy, particularly family physicians and emergency department physicians and nurses who are likely to be contacted by patients outside of clinic hours.

Lastly, for any strategies implemented, it should be recognized that evaluation of effect is essential. Because best practice is not currently defined, the future state must be based on demonstrated improvement in care to patients and more effective service provision.

Implementation Tools

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources*

fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Krzyzanowska MK, Walker-Dilks C, Atzema CL, Morris A, Gupta R, Halligan R, Kouroukis CT, McCann K, Fever Assessment Expert Panel. Approach to fever assessment in ambulatory cancer patients receiving chemotherapy. Toronto (ON): Cancer Care Ontario (CCO); 2015 Nov 27. 67 p. (Program in Evidence-based Care Guideline; no. 12-15). [78 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2015 Nov 27

Guideline Developer(s)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

Guideline Developer Comment

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care (OMHLTC).

Source(s) of Funding

The Program in Evidence-based Care (PEBC) is a provincial initiative of Cancer Care Ontario (CCO) supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by the

PEBC is editorially independent from the OMHLTC.

Guideline Committee

Fever Assessment Working Group

Composition of Group That Authored the Guideline

Authors: M.K. Krzyzanowska, C. Walker-Dilks, C.L. Atzema, A. Morris, R. Gupta, R. Halligan, C.T. Kouroukis, K. McCann, Fever Assessment Expert Panel

Financial Disclosures/Conflicts of Interest

Competing interests in the areas of professional interests were declared by two members; Appendix 1 of the original guideline provides further detail. Individuals with competing interests were not allowed to participate as a member of the Working Group unless otherwise stated. Conflicts of interest (COIs) were managed in accordance with the Program in Evidence-based Care (PEBC) COI Policy .

Guideline Status

This is the current release of the guideline.

The Program in Evidence-based Care (PEBC) guideline, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario (CCO) Web site for details on any new evidence that has emerged and implications to the guidelines.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Cancer Care Ontario (CCO) Web site .

Availability of Companion Documents

The following are available:

Approach to fever assessment in ambulatory cancer patients receiving chemotherapy. Summary. Toronto (ON): Cancer Care Ontario (CCO); 2015 Nov 27. 2 p. Available from the Cancer Care Ontario (CCO) Web site .

Program in Evidence-based Care handbook. Toronto (ON): Cancer Care Ontario (CCO); 2012. 14 p. Available from the CCO Web site .

Program in Evidence-based Care methods handbook. Toronto (ON): Cancer Care Ontario (CCO); 2014 Sep 23. Available from the Program in Evidence-based Care (PEBC) Toolkit Web site .

Program in Evidence-based Care document assessment and review protocol. Toronto (ON): Cancer Care Ontario (CCO); 2015 Apr 16. 13 p. Available from the CCO Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on April 4, 2016.

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